Schizophrenia Research 211 (2019) 108–110

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

The clinical correlation and predictive value of electrophysiological variables on clinical response to clozapine in patients with treatment-resistant schizophrenia

Dear editor,

Although clozapine has been shown to be effective in treatment-resistant schizophrenia (TRS) (Meltzer, 1995), its usage has limitations. It requires a gradual increase in dose during the initiation protocol, a long and costly monitoring and follow-up protocol, interactions with many medicines, frequent life-threatening side effects, a gradual cessation of treatment within 1–2 weeks when discontinued, and high costs for initiating treatment. In addition, it is reported that while assessing the clinical response to clozapine, longer treatment duration is needed than with other antipsychotics, and clinical responses may be observed relatively later (Meltzer et al., 2003). Thus, this situation motivates clinicians to identify patients who may present the best response.

Research on drug response prediction that emphasizes electrophysiological evaluations has the potential to predict treatment response and the clinical outcome of psychiatric disorders (Coburn et al., 2006). Nonetheless there is inconsistency in the findings of electrophysiologic research due to ethnic diversity, different population characteristics, a lack of structured assessment of clinical variables and different outcome definitions.

This study aimed to determine an electrophysiological parameter that can predict the response to clozapine much earlier than the duration required for clinical response. We also proposed to explain the electrophysiological relations of the symptom changes in clinical courses.

1. Methods and results

Twenty-three inpatients who meet both the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) criteria for Schizophrenia and the Kane criteria for treatment resistant schizophrenia were included in the study. They were evaluated by independent psychiatrists in terms of their suitability for clozapine treatment. Written informed consent was obtained from all patients participating in the study and from their relatives. Approvals were obtained from Maltepe University Ethical Committee and the Turkish Ministry of Health. A total of five interviews were performed with the patients: before starting Clozapine, at the first week, the second week, the first month and the sixth month of the treatment. Clinical evaluation scales (Positive and Negative Syndrome Scale, Global Assessment of Functioning) and EEG/ERP monitoring were performed during all five assessments, and a CANTAB schizophrenia battery was used before clozapine and after six months.

The mean dose of Clozapine used by the participants was 320 ± 102 mg/day (min 125, max 600). While 9 patients received Clozapine monotherapy, the others used additional antipsychotics. Two of the patients discontinued medication, while 4 of the patients' medication were replaced by the physician during follow-ups, due to side effects. The PANSS scores of the patients were evaluated retrospectively and the patients who had more than a 25% decrease in total PANSS scores were evaluated as clozapine responsive.

When the subsequent measurements of absolute power changes in the basal EEG activity according to cortical brain regions were examined in the clozapine-responsive group, there were statistically significant differences in the absolute power values of alpha and theta in the frontal and parietal regions. When the baseline and the other values were compared in binary, it was seen that differentiation could be determined from the first month ($p < 0.008$ with Bonferroni correction; respectively p:0.006, p:0.005). In the clozapine non-responsive group there was no significant difference in the absolute power of global basal EEG activities.

Data on event related potentials could not be detected in approximately 25–35% of patients. However, when ERP changes were evaluated after clozapine treatment, there was no change in amplitudes and latencies of P300 obtained from Cz and Pz, P200, N200, N100 potentials from Fz.

A significant relationship was found between the frontal theta absolute power amplitude in the baseline EEG and reaction time in the RTI test (r:0.50, p:0,01). Furthermore, a significant relationship was found to exist between the parietal alpha absolute power amplitude in the baseline EEG and number of token calls starting from a different box in the SWM test (r: −0,46, p:0,03). There was no additional cognitive function associated with regional alpha and theta absolute power values.

Correlation plot of significant relationships with EEG ground activities and treatment responses are shown in Fig. 1.

2. Discussion

Similar to previous studies, an increase in alpha and theta wave activities were observed in frontal and parietal regions (Lacroix et al., 1995) after the initiation of clozapine treatment. There are studies reporting that theta wave activity may originate from the anterior cingulate cortex (Meltzer et al., 2007), medial prefrontal cortex (Onton et al., 2005). Moreover, theta activity is related to cognitive functions such as maintenance of concentrated attention and heightened vigilance (Inanaga, 1998). Nevertheless, some studies emphasize that alpha wave activity in the parietal region is related to spatial and visual WM (Myers et al., 2014; Erickson et al., 2017). This increase in alpha and theta activities after administering clozapine to patients with schizophrenia, which are related to clinical improvement, is thought to reflect an improvement of cognitive functions such as working memory and improvement in response to external stimuli after Clozapine treatment. Furthermore, it is thought that slow wave activity causes a decrease in the corresponding function (Sponheim et al., 2000). Therefore increase in theta activity after administering the medication may imply a reduction in the functionality of an already existing but malignant mechanism.

https://doi.org/10.1016/j.schres.2019.07.021

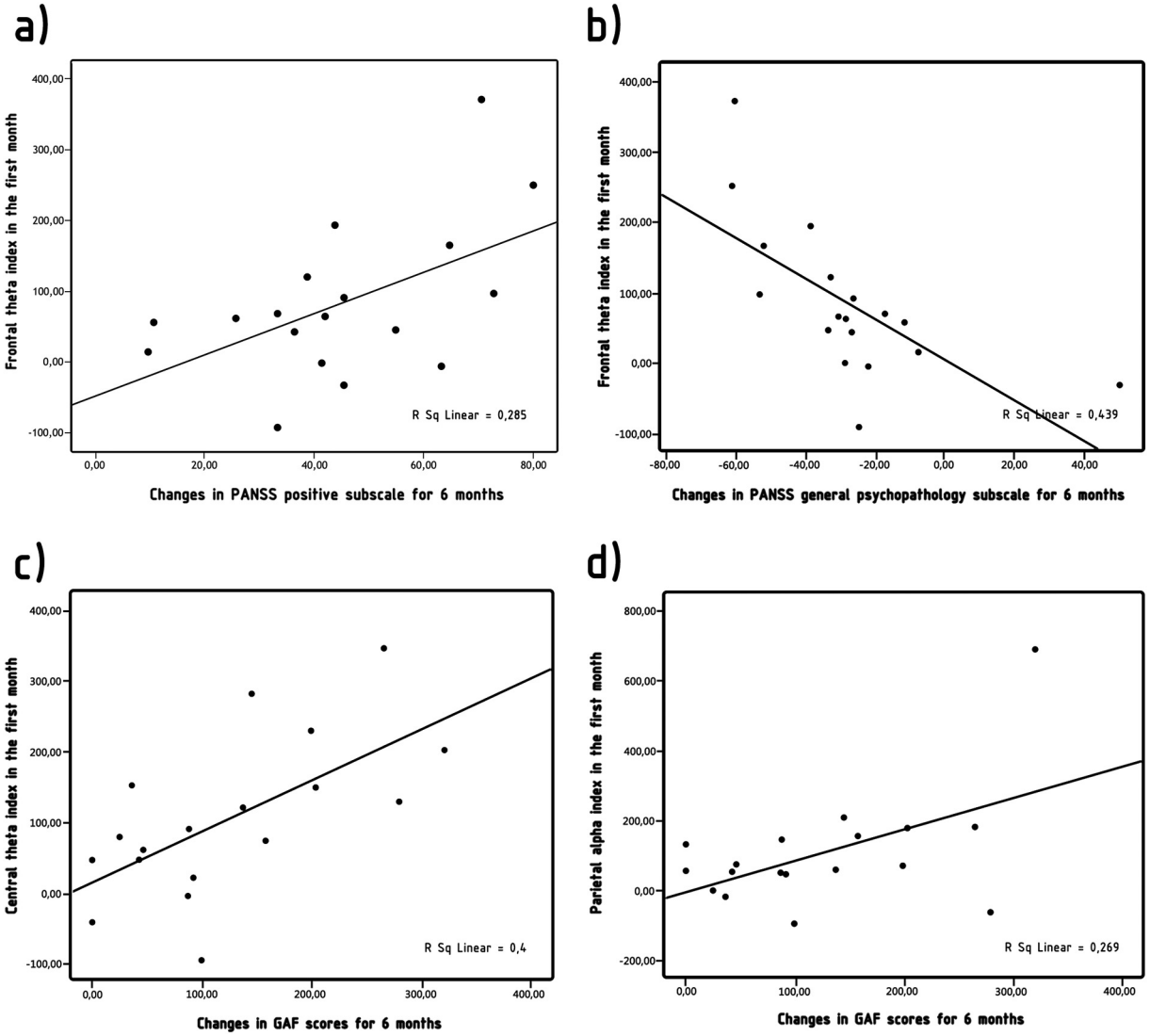

Fig. 1. Correlation plot of significant relationships with EEG ground activities and treatment responses. a–b) A significant correlation was found between the percentage of change observed in PANSS positive subscale and general psychopathology subscale scores, as well as in the percentage of change in the theta wave absolute power values in the frontal region in the first month (respectively rs:0.28, F:6.368, p:0.02 and rs: 0.44, F: 12.513, p:0.003). c–d) As for the percentage of change observed in the GAF scores, there were significant correlations with the change in the theta wave absolute power values in the central region and alpha wave absolute power values in parietal region in the first month (respectively rs:0.40, F:10.670, p:0.005 and rs:0.27, F:5.887, p:0.02).

In conclusion, since an increase in theta and alpha activity was not detected before the clinical response, these findings are likely to be biological indicators of clinical response rather than therapeutic predictability. Testing with appropriate patterned studies is required to determine whether our findings are unique to clozapine or if they apply to other antipsychotic responses.

Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

I would like to thank MD Calli SY. and MD Sever Fidan Y. for their important contributions during data collection.

Author contributions

S. G. contributed to acquisition, analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. A.B. contributed to acquisition, analysis and interpretation; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. B.C.P. contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. H.G. contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

References

Coburn, K.L., Lauterbach, E.C., Boutros, N.N., et al., 2006. The value of quantitative electroencephalography in clinical psychiatry: a report by the Committee on Research of the American Neuropsychiatric Association. J. Neuropsych. Clin. N 18 (4), 460–500.

Erickson, M.A., Albrecht, M.A., Robinson, B., et al., 2017. Impaired suppression of delay-period alpha and beta is associated with impaired working memory in schizophrenia. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2 (3), 272–279.

Inanaga, K., 1998. Frontal midline theta rhythm and mental activity. Psychiatry Clin. Neurosci. 52 (6), 555–566.

Lacroix, D., Chaput, Y., Rodriguez, J.P., et al., 1995. Quantified EEG-changes associated with a positive clinical response to clozapine in schizophrenia. Prog. Neuro-Psychoph. 19 (5), 861–876.

Meltzer, H.Y., 1995. Multiple - outcome criteria in schizophrenia: an overview of outcome with clozapine. Eur. Psychiatry 10 (Suppl. 1), 19–25.
Meltzer, H.Y., Alphs, L., Green, A.I., et al., 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch. Gen. Psychiatry 60, 82–91.
Meltzer, J.A., Negishi, M., Mayes, L.C., et al., 2007. Individual differences in EEG theta and alpha dynamics during working memory correlate with fMRI responses across subjects. Clin. Neurophysiol. 118 (11), 2419–2436.
Myers, N.E., Stokes, M.G., Walther, L., et al., 2014. Oscillatory brain state predicts variability in working memory. J. Neurosci. 4 (23), 7735–7743 34.
Onton, J., Delorme, A., Makeig, S., 2005. Frontal midline EEG dynamics during working memory. Neuroimage 27 (2), 341–356.
Sponheim, S.R., Clementz, B.A., Iacono, W.G., et al., 2000. Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol. Psychiatry 48 (11), 1088–1097.

Sakir Gica
Necmettin Erbakan University, Meram Medical Faculty, Department of Psychiatry, Konya, Turkey
Corresponding author at: Necmettin Erbakan University, Meram Medical Faculty, Department of Psychiatry. Yunus Emre Mah. Beyşehir Cad. No: 281, Konya, Turkey.
E-mail address: sakirgica@hotmail.com.

Ahsen Buyukavsar
Konya Aksehir Public Hospital, Psychiatry, Konya, Turkey

Burc Cagri Poyraz
Istanbul University Cerrahpasa Faculty of Medicine, Department of Psychiatry Istanbul, Turkey

Huseyin Gulec
Istanbul Erenkoy Mental Health and Neurological Disease Education and Research Hospital, Psychiatry, Istanbul, Turkey

7 October 2018